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EXAMINER	
EWOLDT, GERALD R	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/005,073	JEVNIKAR ET AL.	
	Examiner	Art Unit	
	G. R. Ewoldt, Ph.D.	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 April 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *52-102* is/are pending in the application.

4a) Of the above claim(s) *53-58,62,64-68,92-94 and 96-101* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *52,59-61,63,69-91,95 and 102* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. In view of the appeal brief filed on 4/28/10, PROSECUTION IS HEREBY REOPENED. New references in support of the rejections are set forth below.

To avoid abandonment of the application, appellant must exercise one of the following two options:

(1) file a reply under 37 CFR 1.111 (if this Office action is non-final) or a reply under 37 CFR 1.113 (if this Office action is final); or,

(2) initiate a new appeal by filing a notice of appeal under 37 CFR 41.31 followed by an appeal brief under 37 CFR 41.37. The previously paid notice of appeal fee and appeal brief fee can be applied to the new appeal. If, however, the appeal fees set forth in 37 CFR 41.20 have been increased since they were previously paid, then appellant must pay the difference between the increased fees and the amount previously paid.

2. Claims 53-58, 62, 64-68, 92-94, and 96-101 stand withdrawn from further consideration by the Examiner, under 37 C.F.R. § 1.142(b) as being drawn to nonelected species.

Claims 52, 59-61, 63, 69-91, 95, and 102 are being acted upon.

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 52, 59-61, 63, 69-91, 95, and 102 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification's disclosure is insufficient to enable one skilled in the art to practice the invention as claimed without an undue amount of experimentation. Undue

experimentation must be considered in light of factors including: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill in the art, the level of predictability of the art, the amount of direction provided by the inventor, the existence of working examples, and the quantity of experimentation needed to make or use the invention.

Regarding *in vivo* methods which rely on previously undescribed and generally unpredictable mechanisms, "The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art." *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The "amount of guidance or direction" refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling (MPEP 2164.03)." The MPEP further states that physiological activity can be considered inherently unpredictable. The state of the biological arts was such that no methods were available in 1994 for inducing oral tolerance to a transplantation antigen in a human. Indeed, some 15 years later, therapeutic tolerance has not been reproducibly demonstrated to be inducible in humans for the treatment of autoimmune disease or transplant tolerance.

Note that the claims comprise both product and method claims. Also note that only Claims 77 and 83 recite the limitation that the method and products are intended for use in humans. It is clear however, that the products of the claims are intended for just one use, i.e., the induction of oral tolerance to transplantation antigens. And it is also well-known that transplantation is performed almost exclusively in humans. Accordingly, all of the claims under examination are rejected for lack of enablement.

Attempts to induce tolerance in humans have been completely unsuccessful in multiple different documented instances. See for example, *Marketletter* (9/13/99, of record) which teaches the complete failure of tolerance induction in human trials. Both

Myloral (for multiple sclerosis, MS) and Colloral (for rheumatoid arthritis, RA) provided successful results in inducing tolerance in small in-bred animal models, however, both were complete failures in human trials. Also see Pozzilli et al. (2000, of record), wherein the authors demonstrate that, while the induction of tolerance to orally administered insulin for the treatment of diabetes might have been expected, it simply did not occur. The authors could only speculate as to the reasons for the trial's failure. The authors did note one complicating factor that has been reported several times, and will have to be considered in all future work, a large placebo effect wherein both the treated and control subjects showed similar temporary improvement. Three years later Skyler et al. (2005) reported another failure in one of the largest placebo-controlled tolerance trials ever performed in humans (the administration of insulin for the prevention of type 1 diabetes).

Other investigators have gone beyond simply reporting and have tried to consider the reasons for the unexplained problems in establishing human tolerance. See, for example, Dong et al. (1999):

> "Despite the fact that it has been relatively easy to induce true tolerance in small experimental animals, translating these studies into larger animals and humans has been much more difficult to achieve. Some of the hurdles that may explain this dilemma are summarized in Table 3. *Even if we have the ideal strategy to use in humans, the lack of reliable predictable assays for rejection or tolerance still does not allow us to know if a patient is truly tolerant so that immunosuppressive agents may be withdrawn*", (emphasis added).

WO 02/053092 (of record) teaches that the oral administration of antigens for the induction of tolerance presents numerous additional "obstacles", including the problem of accurate dosing given the necessity of digestion which alters both concentration and structure of the antigens. In that work the inventors conclude that:

> "oral and mucosal tolerance cannot be deduced from antigenic activity in conventional immunization, or even *in vitro* results, and must result from extensive empirical experimentation,"

In another attempt to explain these repeated failures Goodnow (2001, of record) states:

> "Obtaining the desired response [tolerance] with these strategies [tolerance induction] is **unpredictable** because many of these signals [tolerogenic] have both tolerogenic and immunogenic roles,"

(see the Abstract). The author goes on to teach that while the induction of oral tolerance might be considered "an attractive notion", the method has failed in humans because of the lack of understanding of the mechanisms involved (page 2120, column 2).

More recently, Kraus and Mayer (2005) looked at tolerance induction in inflammatory bowel disease (IBD). They reported the ease with which tolerance is induced in in-bred experimental mice and contrasted that with the difficulty in inducing tolerance in humans. Speculating on the reasons for the difference the authors considered a lack of dosing optimization but went on to report that *the mechanisms of tolerance induction in humans and mice appear to be fundamentally different*. Most importantly, Kraus and Mayer report a genetic component wherein many IBD patients and their family members appear to be *incapable* of becoming tolerant to oral antigens because they lack the ability to generate the required T regulatory cells. If confirmed, this would mean that *no* tolerance induction regime could work in these patients.

Even more recent work has attempted to duplicate favorable results established in in-bred animal models in a more complex mouse model more realistic to the out-bred human population. See, for example, Bell et al. (2008). The authors employed F_1 hybrid mice (a cross between two in-bred strains) wherein they asked if toleragens that worked in the parent strains would induce tolerance in the crossed F_1 hybrid mice. Unfortunately the results showed that in at least one instance, not only was tolerance not induced, but disease was actually exacerbated. Thus, the work serves as a clear demonstration that the induction of immune tolerance is far from predictable in anything other than carefully chosen in-bred experimental mouse strains.

Even the 20th century mouse models for the study of autoimmune disease and the induction of immune tolerance have recently been called into question. As pointed out by Mark Davis in a recent interview, mice make a "lousy model" for the human immune system. He refers to mice as a short-lived rodent who's immune system has adapted for scurrying around with its nose in the dirt (Leslie, 2010).

As set forth in *Rasmusson v. SmithKline Beecham Corp.*, 75 USPQ2d 1297, 1302 (CAFC 2005), enablement cannot be established unless one skilled in the art, "would accept without question"

an Applicant's statements regarding an invention, particularly in the absence of evidence regarding the effect of a claimed invention. Specifically:

> "As we have explained, we have required a greater measure of proof, and for good reason. If mere plausibility were the test for enablement under section 112, applicants could obtain patent rights to "inventions" consisting of little more than respectable guesses as to the likelihood of their success. When one of the guesses later proved true, the "inventor" would be rewarded the spoils instead of the party who demonstrated that the method actually worked. That scenario is not consistent with the statutory requirement that the inventor enable an invention rather than merely proposing an unproved hypothesis."

A review of the instant specification shows no induction of tolerance and indeed, it is unclear precisely what the examples are intended to demonstrate other than that the asserted autoantigen GAD can be produced in tobacco and potatoes. There are no examples demonstrating any induction of oral tolerance in any model or under any conditions. Interestingly, most the few putative autoantigens even mentioned in the specification have been studied and found to not induce tolerance in humans: myelin basic protein, collagen, insulin, etc. And even less is known about inducing tolerance to the elected species of MHC Class II molecules. Further regarding GAD as a possible human autoantigen because it is an autoantigen in NOD mice. Applicant fails to consider that not even all NOD mouse strains are diabetes susceptible, e.g., NOD H-2^k and NOD DQ8 do not develop the disease whereas H-2 I-A^{g7} mice do. This difference in susceptibility to diabetes of even very closely genetically related mice demonstrates that results derived in a single inbred animal model cannot be readily transferred to the treatment of the entire outbred human population. Most likely the lack of susceptibility of NOD H-2^k and NOD DQ8 to diabetes is related to the differences in their MHCs from the H-2 I-A^{g7} mice (because this is essentially the only difference between the mice), and the peptides that they are capable of presenting. **And note that peptide presentation is an absolutely critical element for the establishment of immune tolerance.** How different then are the literally hundreds of more distantly related and diverse human MHCs and the peptides that they are capable of presenting? How then can it be reasonably predicted that what occurs in just one inbred mouse strain, but not the most closely related other mouse strains, will occur in all unrelated and genetically diverse humans? Also note that it is well-known that tolerance to GAD is **not** effective for the treatment of diabetes in another well established diabetes model, the BB rat, see for example, Petersen et al. (1997). And

further note that Hanlon et al. (1999) establish that GAD is not even an autoantigen in the BB rat animal model of diabetes.

Also consider the simple fact that if all that was required to establish immune tolerance was the oral or enteral administration of antigen, then there would be no food allergies and no allergies to airborne allergens like dust mites and ragweed - everyone would be tolerant because of repeated environmental administration.

Finally consider:

Any analysis of whether a particular claim is supported by the disclosure in an application requires a determination of whether that disclosure, **when filed**, contained sufficient information regarding the subject matter of the claims as to enable one skilled in the pertinent art to make and use the claimed invention (emphasis added) (**MPEP 2164.01 [R5]).**

A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, **at the time the application was filed**, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation (emphasis added) (**MPEP 2164.01(a)).**

Once the examiner has weighed all the evidence and established a reasonable basis to question the enablement provided for the claimed invention, the burden falls on applicant to present persuasive arguments, supported by suitable proofs where necessary, that one skilled in the art would be able to make and use the claimed invention **using the application as a guide** (emphasis added) (**MPEP 2164.05).**

Applicant may submit factual affidavits under 37 CFR 1.132 or cite references to **show what one skilled in the art knew at the time of filing the application.** (emphasis added) (**MPEP 2164.05).**

To overcome a *prima facie* case of lack of enablement, applicant must demonstrate by argument and/or evidence that the disclosure, as filed, would have enabled the claimed invention for one skilled in the art at the time of filing. This does not preclude applicant from providing a declaration after the filing date which demonstrates that the claimed invention works. However, the examiner should

carefully compare the steps, materials, and conditions used in the experiments of the declaration with those disclosed in the application to make sure that they are commensurate in scope; i.e., that the experiments used the guidance in the specification as filed and what was well known to one of skill in the art. **Such a showing also must be commensurate with the scope of the claimed invention, i.e., must bear a reasonable correlation to the scope of the claimed invention (MPEP 2164.05).**

The MPEP makes clear that first, an invention must be enabled at the time of filing, second, the specification itself must teach how to make and use the claimed invention, and third, any showing must be commensurate with the scope of the claimed invention. In the instant case none of these requirements have been met. The induction of oral tolerance was not enabled in humans at the time of filing, the specification fails to disclose any examples of the induction of oral tolerance whatsoever, thus, adding nothing to that which was known in the art at the time of filing, and a review of the extremely broad claims reveals that they encompass the suppressing of *any* type of immune response through the administration of *any* immunosuppressive antigen. Thus, the claims encompass the suppression of a response to a transplant antigen through the administration of a putative autoantigen such as GAD. Clearly, the claims encompass an invention that would fly in the face of scientific reality.

In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. Given that the induction of immune tolerance has been referred to as the seeking of the "Holy Grail" of transplantation (Schroeder et al. (2003)), fraught with difficulties not even considered in the instant specification, further in view of the quantity of experimentation necessary, the lack of sufficient guidance in the specification, the lack of sufficient working examples, i.e., the specification discloses no data relevant to the induction of tolerance, the unpredictability of the art, and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

As set forth previously, the Inventor previously submitted two references, Husby et al. (1994, of record) and McKown et al.

(2000, of record), assertedly teaching the induction of tolerance in humans.

Regarding Husby et al., the reference teaches the reduction of *in vitro* T cell proliferation and delayed skin test responses to KLH. The reference further teaches that no reduction in B cell responses was observed. The authors speculate that it was only a Th1 response that was reduced. Clearly then, the reference cannot enable the broad methods and compositions of the instant claims that recite the suppressing or reducing of *any* type of immune response. Interestingly, the authors point to the clinical studies of Weiner et al. to address the question of whether or not the feeding of antigens can be used to treat MS or RA. It is those very studies that were reported as being stopped in the *Marketletter* reference.

Upon further review of the work of the scientific group of which Husby was a member, Elson et al., it was found that the group reported in 2004 (Moldoveanu et al., of record) the failure of oral tolerance in suppressing an ongoing immune response. Using the same KLH antigen model as used some ten years earlier in Husby et al., the reference states "some form of immunomodulation greater than that provided by the oral administration of antigen alone is required in humans for suppression of an existing immune response". **This would appear to be a direct teaching that the inventions of the instant claims cannot work as broadly claimed.**

Regarding McKown et al., the reference provides encouraging preliminary data indicating that oral administration of type I collagen (CI) might be useful for treating systemic sclerosis (SSc). Note that regarding tolerance, however, the reference teaches only that IFNγ production was reduced which, "suggests that oral tolerance to CI was effected". Note another teaching of the reference, specifically, an unexplainable reduction in IL-10 (which was previously reported to be *upregulated* in other models of oral tolerance). Also note the conclusions of the reference, i.e., "Further evaluation of oral tolerance to CI in patients with SSc is justified," and "Oral CI administration appears to be safe. Its efficacy needs to be assessed by a larger placebo-controlled, double-blind trial". It appears then that even this specific embodiment of the induction of oral tolerance has not risen past the level of idea. Thus, it cannot support the broad inventions of the instant claims.

Upon further review the work of the scientific group including McKown et al., numerous examples in which no sign of oral tolerance induction could be induced can be found. See for example, McKown et al. (1999, of record), in which the authors document the lack of efficacy of the oral administration of type II collagen for the treatment of RA. More interestingly, see Carbone et al. (2004, of record) in which, in this instance, the oral administration of CI had no effect on SSc patients. Given the same group's report of encouraging results with the same composition in the same patients four years earlier in the McKown et al. (2000, of record) reference, it would appear that the group was simply employing methods of trial-and-error (unsuccessfully) in their attempts to induce tolerance in SSc patients. As methods of trial-and-error provide no particular expectation of success with any particular embodiment (as aptly demonstrated here), said methods are considered to be inherently unpredictable and requiring of undue experimentation. Further note that this *demonstration* of unpredictability in 2004 must call into question the enablement of the methods and compositions of the instant claims that claim priority to 1993.

Applicant has submitted Womer et al. (2008, Abstract only), arguing the reference supports the argument that tolerance has been found effective in a number of contexts.

A review of the complete reference reveals that its teachings are not enabling for the scope of the claimed method. First note that only four patients participated in the study (of which just three completed the study), that the study was of just three months' duration, and even then the observed results were only transient. More importantly, the patients were carefully selected for reactivity with the specific alloantigen (HLA-DRB1*1501, page 755) with which they were then dosed (this is presumably why so few patients were found fitting the study criteria, page, 756). Contrast this with the breadth of the claims wherein the patients can be dosed with any human MHC protein (Claim 73) or even any "mammalian transplantation antigen" whatsoever (Claim 72). And even the authors admit, *some 15 years* after the priority date of the instant application, the need for larger, longer studies to establish whether or not their own minimal results are "reproducible" (page 758). Interestingly, the reference demonstrates even more the unpredictable nature of the induction of immune tolerance in humans by supplying no explanation for the observation of a transient loss of response to an unrelated mumps antigen.

Applicant has submitted Ergun-Longmire et al. (2004, of record) in support of the claimed inventions.

The reference provides little if any support for the claimed inventions. Even after picking a very specific subset of patients, i.e., type 1 diabetic patients requiring insulin replacement for less than four weeks, the authors reported, "Disappointingly, there were no clinical benefits discernible from our oral insulin tolerance therapy as reflected in improved diabetes control, lowered glycated hemoglobin levels, or reduced daily insulin dosage," i.e., *the method did not work*.

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 52, 59-61, 63, 69-76, 78-91, 95, and 102 stand/are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 92/07581 (1992, IDS) in view of U.S. Patent No. 5,484,719 (IDS).

Note that as set forth in Section 4, above, while the induction of antigen-specific immune tolerance has not been shown to be reproducible in humans, it has been shown repeatedly in some inbred experimental animal models. Accordingly, while the claimed methods and compositions are unpredictable for use in larger mammals, particularly humans, they are obvious, as set forth below, and there is every expectation of their success for use in experimental animal models.

WO 92/07581 teaches a method (and product) for the induction of tolerance to MHC Class II proteins through the oral administration of an effective immunosuppressive dose of said proteins as a method for suppressing the rejection of engrafted donor tissues in humans (see particularly Summary of Invention, pages 7-8 and Class II MHC molecules pages 11-12).

The reference teaching differs from the claimed invention only in that it does not teach the use of a transgenic plant as the source of the oral tolerizing antigen.

The '719 patent teaches that transgenic plants comprise an inexpensive and convenient source of edible oral vaccines (antigens) (see particularly column 4, lines 7-21). The reference further teaches a DNA construct for transforming a plant comprising a Cauliflower Mosaic Virus 35S promoter (see particularly column 8, lines 41-45) and nopaline synthase termination sequence (see particularly column 9, lines 29-30), and that said vaccines comprise partially purified extracts of leaves, stems, and seeds (see particularly column 6, line 60) of a potato or a tomato (see particularly column 7, lines 10-15).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to perform a method (and produce a product) for the induction of tolerance in animals to MHC Class II proteins through the oral administration of an effective immunosuppressive dose of said proteins as a method for suppressing the rejection of engrafted donor tissues, as taught by WO 92/07581. One of ordinary skill in the art at the time the invention was made would have been motivated to produce the antigen for said tolerance induction in the transgenic plant of the '719 patent comprising a DNA construct for transforming a plant, said construct comprising a Cauliflower Mosaic Virus 35S promoter and a nopaline synthase termination sequence, said antigen further comprising a partially purified extract of leaves, stems, and seeds of a potato or a tomato, because said transgenic plant would have provided an inexpensive and convenient source of said antigen, again as taught by the '719 patent. Note that the '719 patent teaches the administration of oral antigens for the induction of an immune response whereas the instant claims are drawn to the administration of oral antigens for the induction of tolerance. However, the induction of tolerance and the induction of an immune response can be considered two sides of the same coin. Indeed, some immunologists refer to the induction of tolerance as the induction of a suppressive immune response. Thus, the use of a transgenic plant as the source of an antigen for the induction of an immune response renders the use of a transgenic plant as the source of an antigen for the induction of tolerance obvious.

Applicant's arguments, filed 2/03/09, have been fully considered but they are not persuasive. Applicant argues a lack of motivation to combine the references referring to their teachings as "diametrically opposed".

As set forth previously, sound scientific reasoning would lead the ordinarily skilled artisan, in this case an immunologist, to the conclusion that if viral, bacterial, and fungal antigens could be efficiently produced in a plant, so could tolerogenic antigens - there is no teaching of record that tolerogenic antigens differ from any other type of antigens. Antigens are routinely defined as substances capable of inducing an immune response (though technically, "immunogens" is the proper term for antigens capable of inducing an immune response). As set forth previously, WO 92/07581 teaches that tolerance is the induction of a suppressive immune response. Accordingly, this combined knowledge renders the inventions of the instant claims, i.e., compositions and methods for the induction of a suppressive immune responsive comprising administering antigens produced in plants orally, obvious.

Also note the Womer (2008) reference recently submitted by Applicant. The reference makes clear that the antigens for which immune tolerance is sought are the same antigens which are administered orally. This is not a new or unknown concept. The induction of immune tolerance in experimental animals through the feeding of the same antigens that are then used to induce and immune response is a decades old concept. See, for example, Mowat and Parrot (1983). In this work the immune response to ovalbumin (OVA) was studied. Absent immune tolerance, an immune response to OVA is mounted upon vaccination with OVA. But upon feeding the animals OVA before vaccination, with the very same OVA antigen, immune tolerance to the antigen is established (see particularly, Figure 2). Accordingly, Applicant's argument that an ordinarily skilled immunologist would only expect an effect opposite of immune tolerance upon the oral administration of antigens is simply not persuasive.

7. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional

rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

8. Claims 52, 59, and 60 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claims 17-20, 34, and 53 of U.S. Patent Application No. 11/815,359. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the '359 application are drawn to the same method of administering an antigen obtained from a transgenic plant as are the instant claims. Note that while the elected species of antigens are different in the applications (MHC protein versus GAD) the broad independent claims overlap such that the rejection is proper

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Applicant has failed to address this rejection. Applicant is advised that a response to this rejection is required in response to this Office action.

9. Claims 52, 59-61, 63, 69-76, 78-91, 95, and 102 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

As set forth previously, Under *Vas-Cath, Inc. v. Mahurkar* , 19 USPQ2d 1111, 1117 (Fed. Cir. 1991), to satisfy the written description requirement, an applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in *possession* of the invention, and that the invention, in that context, is whatever is now claimed.

There is insufficient written description to show that Applicant was in possession of an "immunosuppressive fragment" of an antigen as is set forth in the claims.

An adequate written description of the immunosuppressive fragments of the claims would require either an adequate description of a common structure and a common function, or a disclosure of a representative number of immunosuppressive fragment species. While some attempt has been made at disclosing a common function, i.e., the fragments are immunosuppressive, there is no discussion of a common structure. Indeed, as the evidence set forth above demonstrates the unpredictable nature of inducing antigen-specific immune tolerance there exists no common tolerogenic structure, i.e., there is no common antigen fragment structure that would render any particular antigen fragment immunosuppressive. This concept is particularly well demonstrated in Bell et al. (2008) wherein the same antigen is tolerogenic in one animal and exacerbates disease in another. Clearly there *is* no tolerogenic fragment in the antigen. Accordingly, the specification must disclose a representative number of species describing the claimed genus of immunosuppressive fragments. Given that no such fragments are disclosed in the instant specification, one of skill in the art would conclude that the specification fails to disclose either a representative number of species, or common functional and structural characteristics, adequate to describe the claimed genus of immunosuppressive antigen fragments. See *Eli Lilly*, 119 F.3d 1559, 43 USPQ2d 1398.

10. No claim is allowed.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Gerald Ewoldt whose telephone number is (571) 272-0843. The examiner can normally be reached Monday through Thursday from 7:30 am to 5:30 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ram Shukla, can be reached on (571) 272-0735.

12. **Please Note:** Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197.

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A Supervisory Patent Examiner (SPE) has approved of reopening prosecution by signing below:

/Ram R. Shukla/
Supervisory Patent Examiner, Art Unit 1644